Synopsis – Study 16305A

Study Title A clinical study of patients with symptomatic neurogenic orthostatic hypotension to assess sustained effects of droxidopa therapy
Investigators 29 principal investigators at 29 sites in 2 countries *Signatory investigator* – [redacted]
Study Sites 29 sites – 2 in Canada and 27 in the United States
Publications None (as of the date of this report).
Study Period *First patient first visit* – 19 November 2013 (the date when the first *Informed Consent Form* was signed) *Study terminated* – 20 October 2014 *Last patient last visit* – 23 December 2014 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – To evaluate the clinical efficacy of droxidopa *versus* placebo, as demonstrated by improvements in dizziness (Orthostatic Hypotension Symptom Assessment [OHSA] Item 1 score) from randomisation over a 12-week (maximum) treatment period in patients with symptomatic neurogenic orthostatic hypotension (nOH) (primary objective added [Protocol Amendment 1]) • *Secondary objectives*: – To evaluate the clinical efficacy of droxidopa *versus* placebo using endpoints derived from the Orthostatic Hypotension Questionnaire (OHQ), Clinical Global Impression – Global Improvement (CGI-I), Clinical Global Impression – Severity of Illness (CGI-S), and Boston University Activity Measure For Post-Acute Care (AM-PAC) Basic Mobility Outpatient Short-form Questionnaires, as well as assessment of patient-reported falls, and blood pressure measurements during the Orthostatic Standing Test (OST) – To evaluate the safety of droxidopa *versus* placebo by adverse events, vital signs, electrocardiograms (ECGs), and clinical safety laboratory tests (secondary objectives added [Protocol Amendment 1])

Study Methodology

- This was an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, double-blind study.
- The study design is in Figure 1 and the procedures and assessments conducted during this study are summarised in Figure 2.
- The study consisted of a 2-week (maximum) screening period, followed by a 2-week (maximum) open-label titration period (OL Period), a 3-week (maximum) washout period, and a 12-week double-blind treatment period (DB Period). During the titration period, patients received 100, 200, 300, 400, 500, or 600 mg droxidopa t.i.d. to achieve an optimal dose for each patient. During the double-blind treatment period, only one dose reduction was allowed and no dose increase was allowed (clarified that dose increase was not allowed during the double-blind treatment period [Protocol Amendment 2]).
- At randomisation, patients had to have an OHSA Item 1 score of ≥3 and ≥50% of the baseline score on the OHSA Item 1 score to be eligible to continue into the double-blind treatment period. Patients were stratified to receive droxidopa or placebo (1:1) according to two factors:
  - the number of patient-reported falls during the OL Period and the washout period (patients who did not fall, patients who fell 1-10 times, and patients who fell >10 times)
  - region: United States and Non-United States (stratification by region added [Protocol Amendment 1])
- Data on patient falls were collected daily using an interactive voice response system diary. A fall was defined as "unexpectedly coming to rest on the ground, floor, or just a lower level than where you started." Patients who reported falling in the previous 24 hour were asked additional questions about the fall(s), including whether or not they sustained any fall-related injuries. The daily diary was to be reviewed at each study visit for any adverse events related to reported fall-related injuries.
- Efficacy and safety data were collected throughout the study.
- A safety follow-up (visit or telephone call) was scheduled for 4 weeks after completion of the double-blind treatment period or after withdrawal from the study.
- The recruitment into Study 16305A has been stopped due to potential interference/competition with a post-marketing study for droxidopa which was requested by the United States Food and Drug Administration.
- At the time of study termination, patients who had not yet taken the first dose of investigational medicinal product (IMP; that is, who completed only Visit 1 and/or Visit 2) were withdrawn immediately. Patients active in the titration period were allowed to complete titration with droxidopa (if the investigator and patient agreed) and the final titration visit was considered an Early Termination Visit. Patients active in the washout period were withdrawn and requested to come in for an Early Termination Visit. Patients active in the double-blind treatment period were required to come in for an Early Termination Visit within 4 weeks of study termination; patients who had completed Visit 7 were allowed to complete participation in the study (if the investigator and patient agreed). All patients who had taken at least one dose of IMP at the time of study termination were also required to have a Safety Follow-up contact within 4 weeks of their last on-site visit.

Number of Patients Planned

450 patients were planned for randomisation: 225 in the placebo group and 225 in the droxidopa group. The randomisation list, including patient identifier and treatment assigned are in Listing 1.4.3. Patients are identified throughout this report by their screening number.

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of symptomatic orthostatic hypotension associated with primary autonomic failure (Parkinson's disease, multiple system atrophy, or pure autonomic failure) or dopamine beta-hydroxylase deficiency, who:

- had an OHSA Item 1 score ≥4 at the Baseline Visit
- had a decrease of ≥20 mmHg in systolic blood pressure within 3 minutes of standing at the Baseline Visit
- were ≥18 years of age and ambulatory, defined as being able to walk ≥10 metres

Investigational Medicinal Product, Doses and Mode of Administration, Batch Numbers

Droxidopa – 300, 600, 900, 1200, 1500, or 1800 mg/day, capsules, orally, batch Nos. L0404996 and L0405081 (100 mg); L0405022 and L0405076 (200 mg); and L0405033 (300 mg)

Reference Therapy, Doses and Mode of Administration, Batch Numbers *Placebo* – capsules, orally, batch Nos. L0405083 (100 mg); L0405024 (200 mg); and L0405026 (300 mg)
Duration of Treatment Up to a total of 14 weeks
Efficacy Assessments • OHQ • Daily assessment of dizziness/lightheadedness • OST • CGI-I • CGI-S • AM-PAC Basic Mobility Outpatient Short Form questionnaire • Patient-reported falls
Safety Assessments Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, ECGs, and physical examinations
Endpoints • Primary endpoint: – OHSA Item 1 score at each visit and change from randomisation to each post-randomisation visit • Secondary endpoints: – clinician-rated and patient-rated CGI-S score at each visit – clinician-rated and patient-rated CGI-I score at each visit – blood pressure during OST at each visit and the change from randomisation to each post-randomisation visit

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of IMP in either the open-label period or the double-blind period
  - *open-label APTS* (OL-APTS) – all patients who took at least one dose of droxidopa during the open-label titration period
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *double-blind APTS* (DB-APTS) – all patients in the APRS who took at least one dose of IMP during the double-blind treatment period. Patients were analysed according to the actual treatment received
  - *full-analysis set* (FAS) – all patients in the APRS who took at least one dose of IMP during the double-blind treatment period. Patients were analysed according to the treatment assigned at randomisation
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- The efficacy and safety data were summarised using summary statistics (n, arithmetic mean, standard deviation, median, minimum, and maximum) for continuous variables, and counts and percentages for categorical variables.
- The number of patients who withdrew from treatment and the primary reason for withdrawal were summarised.
- Compliance with the IMP was defined as taking between ≥80% and ≤120% of the planned doses during the double-blind treatment period.
- The following definitions were used to classify adverse events:
  - OL-APTS adverse event – an adverse event that starts at or after the start of the open-label period and prior to the start of the Randomisation Visit
  - DB-APTS adverse event – an adverse event that starts or increases in intensity at or after the start of the Randomisation Visit
- Adverse events were summarised by system organ class (SOC) and preferred term, by intensity, and by relationship to IMP; the incidences of serious adverse events (SAEs) and adverse events leading to withdrawal were summarised by SOC and preferred term. Adverse events reported more than once in the same patient were counted only once in a period, and at the maximum intensity reported. Adverse events for which information on intensity and relationship was missing were classified as *severe* and considered *related* to IMP, respectively.
- For AEs related to falls, the database was searched using the following MedDRA terms: arthralgia, back pain, conjunctival haemorrhage, contusion, excoriation, face oedema, facial bones fracture, fall, fibula fracture, foot fracture, headache, injury, joint sprain, laceration, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, neck pain, non-cardiac chest pain, pain, pain in extremity, skin laceration, skin lesion, tooth fracture, traumatic brain injury, and traumatic haematoma.
- Absolute values and changes from baseline to each assessment in clinical safety laboratory tests, vital signs, and ECG parameters were summarised using descriptive statistics. For blood pressure measurements taking during the OST, the incidence of systolic blood pressure (SBP) ≥160 mmHg, ≥180 mmHg, ≥200 mmHg, diastolic blood pressure (DBP) ≥110 mmHg and ≥120 mmHg were tabulated. The change in heart rate measurements taking during the OST was summarised. Changes in QT_{cB}/QT_{cF} ≥30 msec and ≥60 msec, and frequencies of patients with QT_{cB}/QT_{cF} ≥450 msec, ≥480 msec, and ≥500 msec were tabulated.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Open-label Titration Period		Double-blind Treatment Period					
	Droxidopa		Placebo		Droxidopa		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients screened	114							
Patients treated (APTS)	61							
Patients withdrawn	16							
Patients randomised (APRS):			23		22		45	
Patients treated (APTS)			23		22		45	
Patients completed			10	(43.5)	11	(50.0)	21	(46.7)
Patients withdrawn			13	(56.5)	11	(50.0)	24	(53.3)
Primary reason for withdrawal:								
Adverse event(s)	6	(9.8)	1	(4.3)	1	(4.5)	2	(4.4)
Non-compliance with IMP	0		1	(4.3)	0		1	(2.2)
Study termination	3	(4.9)	7	(30.4)	7	(31.8)	14	(31.1)
Withdrawal by patient	1	(1.6)	3	(13.0)	2	(9.1)	5	(11.1)
Other	6	(9.8)	1	(4.3)	1	(4.5)	2	(4.4)
Analysis sets:								
OL-APTS	61	(100)						
DB-APTS			23	(100)	22	(100)	45	(100)
FAS			23	(100)	22	(100)	45	(100)

Cross-reference: Table 1.1.1

- In the open-label titration period, the most common primary reasons for withdrawal were: adverse event and other reasons (9.8% each). The most common adverse event leading to withdrawal was *supine hypertension* (3 patients; Listing 1.4.2). The most common other reason for withdrawal was because patients met the titration stopping criteria (sustained supine hypertension or unable to tolerate side effects considered *related to* IMP; 4 patients; Table 1.1.1).
- In the double-blind treatment period, the most common primary reason for withdrawal was due to study termination by sponsor (approximately 31% in both treatment groups; Table 1.1.1). Individual patient disposition and primary reason for withdrawal are in Listing 1.4.2.

Demography and Baseline Characteristics of the Study Population

- Due to study termination, only 10% of the planned number of patients was randomised to treatment and only half of them completed the 12-week treatment period.
- Demographics and other baseline characteristics are summarised in Table 1.1.2. The mean age was 70 years (range: 48 to 84 years), 64% were men, and 96% were White.
- 73% of the patients had a primary diagnosis of Parkinson's disease (Table 1.1.2). 76% in both treatment groups were receiving dopa decarboxylase inhibitors (Table 1.1.2). Individual patient demographics and baseline diagnoses are in Listing 1.4.1.
- The most common (>40%) recent and concomitant medications taken by patients in the open-label titration and double-blind treatment periods were (Table 1.1.3):
  - dopa and dopa derivatives (74% in the titration period; 78% in the placebo group, 68% in the droxidopa group in the double-blind treatment period)
  - mineralocorticoids (56% in the titration period; 57% in the placebo group, 59% in the droxidopa group in the double-blind treatment period)
- Regarding midodrine, it should be noted that patients taking midodrine did so only during the screening period (as per protocol) or during the safety follow-up period.

Exposure

- During the 12-week double-blind treatment period, the majority of the patients in both treatment groups received 600 t.i.d. dose (65% and 73% in the placebo and droxidopa groups, respectively; Table 1.1.4). The mean duration of exposure to IMP was 57 days and 65 days in the placebo and droxidopa groups, respectively, and IMP compliance was 97% and 87% in the placebo and droxidopa groups, respectively (Table 1.1.4). The mean duration of exposure to droxidopa during the open-label titration period was 7 days.

Efficacy Results

- The OHSA Item 1 score results are summarised below:

	Placebo		Droxidopa		Mean difference from placebo (95% CI)
	n	Mean ± SD	n	Mean ± SD	
Randomisation	23	5.6 ± 1.8	22	6.2 ± 1.9	
Week 1	20	5.2 ± 2.0	22	5.1 ± 2.7	
Week 12	10	5.0 ± 2.3	11	5.2 ± 2.9	
Change from randomisation to Week 1	20	-0.5 ± 1.8	22	-1.1 ± 3.2	-0.6 (-2.3, 1.0)
Change from randomisation to Week 12	10	-0.6 ± 1.7	11	-0.7 ± 2.8	-0.1 (-2.3, 2.0)

Cross-reference: Table 1.2.1
CI: confidence interval; SD: standard deviation

- Due to the small number of patients, it was not possible to make any meaningful conclusions.
- The change from randomisation to Week 1/Week 12 in dizziness (OHSA Item 1 score) are summarised in Table 1.2.1. The absolute dizziness score at each time point of assessment is summarised in Table 1.2.2.
- Clinician- and patient-rated CGI-S scores are summarised in Table 1.2.3 and Table 1.2.4, respectively.
- Clinician- and patient-rated CGI-I scores are summarised in Table 1.2.5 and Table 1.2.6, respectively.
- Mean values and changes from randomisation in SBP and DBP during the OST are summarised in Table 1.2.7 and Table 1.2.8, respectively. Changes in SBP and DBP during the OST in the open-label titration and double-blind treatment periods are summarised in Table 1.2.9 and Table 1.2.10, respectively.

Safety Results

- The adverse event incidence is summarised below:

	Open-label Titration Period			Double-blind Treatment Period					
	(N=61)			Placebo (N=23)			Droxidopa (N=22)		
	n	(%)	E	n	(%)	E	n	(%)	E
Any adverse events	34	(55.7)	62	13	(56.5)	29	16	(72.7)	34
Serious adverse events	3	(4.9)	3	3	(13.0)	4	1	(4.5)	2
Action taken with IMP									
Dose increased	3	(4.9)	10	1	(4.3)	1	0		0
Dose not changed	21	(34.4)	29	11	(47.8)	21	12	(54.5)	24
Dose reduced	7	(11.5)	10	0		0	1	(4.5)	1
Dose interrupted	1	(1.6)	1	0		0	0		0
IMP withdrawn	6	(9.8)	6	1	(4.3)	1	1	(4.5)	1
Not applicable	5	(8.2)	6	3	(13.0)	6	5	(22.7)	8
Relationship to IMP									
Not related	20	(32.8)	27	11	(47.8)	27	12	(54.5)	20
Related	23	(37.7)	35	2	(8.7)	2	6	(27.3)	14
Severity									
Mild	26	(42.6)	41	8	(34.8)	17	11	(50.0)	20
Moderate	13	(21.3)	18	6	(26.1)	9	7	(31.8)	12
Severe	3	(4.9)	3	3	(13.0)	3	1	(4.5)	2

Cross-reference: Table 1.3.1

Adverse Events

- Due to the small number of patients, it was not possible to make any meaningful conclusions.
- All adverse events are in Listing 1.4.4.
- During the open-label titration period, 34 patients had 62 events. In the double-blind treatment period, the number of patients who reported any adverse event was 13 and 16 in the placebo and droxidopa groups, respectively. A total of 7 patients had SAEs: 3 patients in the open-label titration period and 4 patients in the double-blind treatment period. No deaths occurred during the study.
- Adverse events with an incidence >5% is summarised below:

	Open-label Titration Period			Double-blind Treatment Period					
	(N=61)			Placebo (N=23)			Droxidopa (N=22)		
	n	(%)	E	n	(%)	E	n	(%)	E
Dizziness	3	(4.9)	3	0		0	2	(9.1)	2
Fatigue	0		0	0		0	2	(9.1)	2
Headache	5	(8.2)	5	1	(4.3)	1	1	(4.5)	1
Hypertension	6	(9.8)	6	0		0	3	(13.6)	3
Laceration	1	(1.6)	1	2	(8.7)	2	2	(9.1)	6
Nausea	4	(6.6)	5	0		0	0		0
Orthostatic hypotension	1	(1.6)	1	2	(9.7)	2	0		0
Urinary tract infection	1	(1.6)	1	3	(13.0)	3	1	(4.5)	1

Cross-reference: Table 1.3.2

- Adverse events with an incidence >5% in the open-label titration period were: *headache* (8.2%), *hypertension* (9.8%), and *nausea* (6.6%). Adverse events with an incidence >5% in either treatment group in the double-blind treatment period were (placebo *versus* droxidopa): *dizziness* (0 *versus* 9.1%), *fatigue* (0 *versus* 9.1%), *hypertension* (0 *versus* 13.6%), *laceration* (8.7% *versus* 9.1%), *orthostatic hypotension* (8.7% *versus* 0), and *urinary tract infection* (13% *versus* 4.5%).

- In the open-label titration period, 3 patients had 3 *severe* adverse events. In the double-blind treatment period, 3 patients had 3 *severe* adverse events in the placebo group and 1 patient had 2 *severe* adverse events in the droxidopa group (Table 1.3.3). None of the *severe* adverse events occurred in ≥1 patient. All patients had recovered from the adverse events (Listing 1.4.4).
- Adverse events considered related to IMP were reported in 23 and 8 patients in the open-label titration period and the double-blind period, respectively (Table 1.3.4). In patients who had adverse events considered *related* to IMP during the double-blind treatment period, the majority were single events reported in individual patients. *Related* adverse events in ≥3 patients were all reported in the open-label titration period: *dizziness* (3 patients [4.9%]), *headache* (4 patients [6.6%]), *hypertension* (6 patients [9.8%]), and *nausea* (4 patients [6.6%]).
- In the open-label titration period, 3 patients had 3 SAEs; in the double-blind treatment period, 3 patients had 4 SAEs in the placebo group, and 1 patient had 2 SAEs in the droxidopa group (Table 1.3.7); none of the SAEs occurred in ≥1 patient and only *acute renal failure* (placebo group) was considered by the investigator to be *possibly related* to IMP (Table 1.3.7, Listing 1.4.7). In addition, the sponsor considered *acute pancreatitis* to be *possibly related* to IMP; the patient (Patient 103001) was withdrawn (Listing 1.4.5). All patients had recovered from the SAEs. For further details, refer to the individual narratives in *Narratives of Serious Adverse Events*.
- All adverse events related to falls during the screening, open-label titration (10 events), and double-blind treatment periods (5 and 10 events in the placebo and droxidopa groups, respectively) were either *mild* or *moderate* and none were SAEs (Listing 1.4.8). The adverse events related to falls that were considered *related to* IMP were: *contusion* (2 events), *headache* (5 events), and *laceration* (6 events). Of note, during the safety follow-up period, 1 patient (Patient 102001) reported a serious adverse event of *intracranial haemorrhage* secondary to a fall that occurred 3 days after discontinuing droxidopa. For further details, refer to the individual narratives in *Narratives of Serious Adverse Events*.
- For the majority of the patients with adverse events, the dose of IMP remained unchanged (Table 1.3.1).
- In the open-label titration period, the most common adverse events leading to withdrawal was *hypertension* (3 patients); all the events of *hypertension* were considered *related* to droxidopa (Table 1.3.5, Listing 1.4.5). In the double-blind treatment period, 1 patient in each treatment group had an adverse event leading to withdrawal; 1 patient (placebo group) had *orthostatic hypotension*, which was considered *not related* to IMP and 1 patient (droxidopa group) had *blood creatine phosphokinase increased*, which was considered *related* to IMP (Table 1.3.5, Listing 1.4.5). All adverse events leading to withdrawal were *mild* or *moderate* and all patients recovered from the events (Listing 1.4.5).
- The dose of droxidopa was reduced in 7 patients who had adverse events in the open-label titration period; the most common adverse events which resulted in droxidopa dose reduction were *hypertension* and *dizziness*, all of which were considered *related* to droxidopa (Table 1.3.6, Listing 1.4.6). In the double-blind treatment period, only 1 patient had an adverse event which resulted in dose reduction (*hypertension* in the droxidopa group; Table 1.3.6); the event was considered *related* to IMP by the investigator (Listing 1.4.6).

Clinical Safety Laboratory Tests

- There were no apparent patterns or trends in the clinical safety laboratory values.
- The haematology parameter values are summarised in Table 1.3.8. Shifts in haematology parameter values are summarised in Table 1.3.9 and Table 1.3.10 for the open-label titration and double-blind treatment periods, respectively.
- The clinical chemistry parameter values are summarised in Table 1.3.11. Shifts in clinical chemistry parameter values are summarised in Table 1.3.12 and Table 1.3.13 for the open-label titration and double-blind treatment periods, respectively.
- The urinalysis parameter values are summarised in Table 1.3.14. Shifts in urinalysis parameter values are summarised in Table 1.3.15 and Table 1.3.16 for the open-label titration and double-blind treatment periods, respectively.
- Individual clinical safety laboratory test results and urinalysis parameter values that were flagged as abnormal (outside the reference range) are in Listing 1.4.9.

Vital Signs

- The mean changes from randomisation in vital signs parameter values (blood pressure, pulse, respiratory rate, and temperature) and heart rate during the OST are summarised in Table 1.3.17 and Table 1.3.18, respectively.
- At the end of study visit (Visit 8 or early termination), the number of patients who had supine hypertension according to the pre-defined cut-off was:
  - SBP ≥160 mmHg: 3 patients each in the placebo and droxidopa groups (Table 1.3.21)
  - SBP ≥180 mmHg: 1 patient in the placebo group (Table 1.3.20).
- No patients had SBP ≥200 mmHg or DBP ≥110 mmHg or DBP ≥120 mmHg at the end of study visit in either treatment group (Table 1.3.19, Table 1.3.22 and Table 1.3.23, respectively).

ECG Values

- ECG values and the changes from baseline are summarised in Table 1.3.24.
- The proportion of patients who had change in QT_{cB} or QT_{cF} ≥30 or ≥60 msec from screening are summarised in Table 1.3.25 and Table 1.3.26, respectively. No patients had change in QT_{cB} or QT_{cF} ≥60 msec (Table 1.3.26) and ≤2 patients had change in QT_{cB} or QT_{cF} ≥30 msec (Table 1.3.25).
- No patients had QT_{cB} or QT_{cF} intervals ≥480 or ≥500 msec at screening or at end of study (Table 1.3.27). In the open-label titration period, the proportion of patients who had QT_{cB} interval ≥450 msec was 21% and 3.3% at screening and at end of study, respectively; the proportion of patients who had QT_{cF} ≥450 msec was 13% and 3.3% at screening and at end of study, respectively. In the double-blind treatment period, ≤5 patients had QT_{cB} or QT_{cF} ≥450 msec at screening or at end of study in either treatment group.

Conclusions

- This study was prematurely terminated.
- The limited sample size precludes meaningful conclusions on the efficacy or safety of droxidopa in patients with symptomatic neurogenic hypotension.

Report Date

28 September 2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.